

## REMARKS

Claims 7-10 and 12 - 26 are pending. New claims 25 and claims 26 are supported on page 7, lines 25 – 34, page 12, lines 5 – 17, and page 43, line 8.

No new matter is added by this amendment.

- I. Claims 7-10 and 12-24 have been rejected under 35 USC §112, first and second paragraphs. The examiner has based these rejections on the language in claims 7, 12 and 13 and new claims 18, 23 and 24 which recite “wherein the recombinant AAV is at least as free of the contaminating adenoviral helper virus as is obtained by subjecting said recombinant AAV to four rounds of cesium chloride gradient centrifugation”. The examiner reiterates that the specification does not provide written support in the specification as what would be the contaminating levels of adenoviral helper virus after four rounds of cesium chloride centrifugation.

Applicants respectfully traverse this rejection.

The relevant question is whether there is sufficient written description to inform a skilled artisan that Applicants were in possession of the claimed invention as a whole at the time the application was filed.

The specification teaches that the rAAV is purified to a level that it is substantially free of contamination with helper adenovirus, such that undesirable immune responses are avoided. The specification teaches that this level of purity can be achieved by appropriate purification means known to one of skill in the art.

Subjecting the rAAV of the invention to four rounds of cesium chloride gradient centrifugation is a means by the inventors removed adequate amounts of contaminating adenoviral helper to avoid undesirable immune responses. The specification teaches how to purify rAAV by performing four rounds of cesium chloride gradient centrifugation. The invention further describes a method of detecting the amount of contaminating adenovirus in a rAAV preparation. See, page 35, lines 1-5. Additionally, methods for detecting antibody responses and cytotoxic immune responses were known in the art as of the filing date of the application. Some of these techniques are described in the application. See, e.g., Figs. 5A-9; page 9, lines 20-30; and throughout the specification.

Applicants submit that one of skill in the art upon reviewing the specification would have possession of the claimed invention, as of the filing date of the application.

Applicants submit that the claimed subject matter is enabled and definite.

Reconsideration and withdrawal of these rejections is requested.

II. Double Patenting

Claims 7-10 and 12-24 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of US Patent No. 5,866,552; provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 9, 20, 21, 23, 25, 26 and 27 of co-pending Application No. 09/237,064 and claims 18-24, 26-28, and 30-35 of co-pending Application No. 09/242,977.

Applicants agree to file a terminal disclaimer over the '552 patent. Applicants also agree to file terminal disclaimers with respect to co-pending application US Patent Application No. 09/242,977, contingent upon the provisional nature of the rejection being removed prior to issuance of this application.

III. Claims 7-10, 18 and 23 are rejected under 35 USC §102(e) as being anticipated by Podsakoff et al, US Patent 5,858,351.

Applicants respectfully traverse this rejection.

Podsakoff does not teach or suggest rAAV with a level of purity as is achieved by at least four rounds of cesium chloride gradient centrifugation. Nor does Podsakoff teach that contamination of rAAV preparations with helper adenovirus can lead to an undesirable immune response.

As previously stated, Podsakoff teaches purification methods directed to inactivating adenovirus function, including heat inactivation. *Thus, Podsakoff is concerned with abrogating replication (inactivating virus).* Podsakoff does not teach rAAV purification to a level which removes of the physical presence of adenoviruses to a level which avoids the undesirable immune response caused by adenoviruses following intramuscular administration.

The inventors have found that the presence of helper adenovirus causes activation of an undesired immune response (even if inactivated). Thus, the present invention teaches purification of rAAV to remove the contaminating adenoviral helper virus to a level which avoids the undesirable immune response to adenoviruses.

For these reasons, applicants request withdrawal of the rejection.

#### IV. Rejections Under 35 USC §103

Despite the fact that the prior art is relied upon for teaching the administration of rAAV, the methods described therein are not sufficient to remove helper adenoviruses, but only to destroy their ability to infect and/or express adenovirus proteins. Thus, the cited prior art documents are not enabling for rAAV purified of helper adenoviruses. Further, because the prior art fails to recognize the presence of contaminating adenoviruses (or their proteins) in their rAAV preparations, it fails to recognize the problems associated with the immunogenicity of helper adenoviruses and their ability to raise an inflammatory response in the subject upon intramuscular injection. For these reasons, the prior art fails to teach or suggest the present invention.

- A. Claims 7-10 and 18-24 have been rejected under 35 USC §103(a) as being unpatentable over Podsakoff, in view of Kashyap, *J. Clin. Invest.*, **96**:1612-1620 (1995).

Applicants respectfully traverse this rejection.

What continues to be missing from the combination of Podsakoff and Kashyap is any recognition that contamination of rAAV preparations with helper adenovirus can lead to an undesirable immune response. Absent this recognition, the cited combination of prior art fails to support the rejection.

With respect to Podsakoff, Podsakoff does not teach or suggest rAAV with a level of purity as is achieved by at least four rounds of cesium chloride gradient centrifugation. Nor does Podsakoff teach that contamination of rAAV preparations with helper adenovirus can lead to an undesirable immune response.

Kashyap contains no teaching regarding the use of such a rAAV vector. The combined teachings of Podsakoff and Kashyap fail to recognize the level of purity from contamination with adenoviral helper necessary for an rAAV to obtain the results provided by the present invention. Thus, even if the teachings of these references are combined as suggested by the examiner, the present invention is not obvious.

It is only the inventors who have recognized the significance of eliminating adenoviral contamination *and not just contamination by adenoviral function* which led to the present invention.

The combined teachings of the cited documents do not teach or suggest the present invention.

For these reasons, even if combined, Podsakoff and Kashyap fail to suggest the present invention.

Reconsideration of this rejection is requested.

- B. Claims 7-20 and 18-24 have been rejected under 35 USC §103(a) as being unpatentable over Podsakoff, in view of Fang, Hu Gene Therapy, 6:1039-1044 and Kay et al, US Patent 5,980,886.

Applicants respectfully traverse the rejection.

Applicants are the first to note that preparations of rAAV produced with helper virus, and particularly Ad helper virus, when injected intramuscularly, induced undesirable immune responses. No combination of the cited documents recognizes the presence of the undesirable immune response in an rAAV preparation contaminated by helper virus, much less provides a solution which avoids such an immune response.

Reconsideration and withdrawal of the rejection is requested.

The Director of the US Patent and Trademark Office is hereby authorized to charge any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees to Deposit Account No. 08-3040.

Respectfully submitted,  
HOWSON AND HOWSON  
Attorneys for the Applicants

By Cathy A. Kodroff  
Cathy A. Kodroff  
Registration No. 33,980  
Spring House Corporate Center  
Box 457  
Spring House, PA 19477  
Telephone: (215) 540-9210  
Telefacsimile: (215) 540-5818